II. THE OBVIOUSNESS REJECTION

Claims 48-59 and 62-68 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Page et al (1997) in combination with U.S. 6,316,426 to von Borstel et al. This rejection is respectfully traversed.

The invention as claimed is directed to a method for treating a congenital mitochondrial disease selected from the group consisting of Mitochondrial Encephalomyopathy, Lactic Acidemia, and stroke like episodes; Lerber's Hereditary Optic Neuropathy; Myclonic Epilepsy and "Ragged Red" (muscle) Fibers; Mitochondrial neurogastrointestinal encephalomyopathy; Neurogenic muscle weakness, Ataxia and Retinitis Pigmentosa; Progressive External Ophthalmoplegia; Leigh's Disease; and Kearns-Sayres Syndrome in a mammal, by administering to the mammal in need thereof an effective amount of a pyrimidine nucleotide precursor.

Page uses uridine to treat four patients having a rare disease associated with excess activity of the enzyme 5'-nucleotidase (an enzyme involved in degradation of nucleotides). In scientific publications describing these patients (*see*: Page, et al., Adv. Exp. Med. Biol. 1998; 431:789-92 and Page et al., Adv. Exp. Med. Biol. 1991;309B:345-8, copies of record), there is no disclosure or suggestion of mitochondrial respiratory chain dysfunction acting as a molecular basis for cytosolic 5'-nucleotidase excess. Page's finding that nucleotide precursors (uridine or ribose) are clinically useful in treating a disorder in which the only known molecular deficit is an excess of an enzyme (5'-nucleotidase) involved in nucleotide degradation would **not**, therefore, have led one of ordinary skill to suspect that uridine or ribose would be useful

in treating conditions caused by mitochondrial respiratory chain dysfunction, even those which might manifest some similar symptoms.

Von Borstel does not cure the above-noted deficiencies of Page. Von Borstel discloses that acylated ribonucleoside derivatives are effective in treating a number of disorders that involve functional impairments in tissue and organ systems involving metabolic deficiencies. Even if one of ordinary skill would have been motivated to combine Page and von Borstel to treat 5'-nucleotidase excess (it is believed one of ordinary would **not** have been so motivated), one of ordinary skill would still **not** have arrived at the claimed invention of treating pathophysiological consequences of mitochondrial respiratory chain dysfunction. Accordingly, no *prima facie* case of obviousness has been established in this case.

On page 4 of the Action, it is stated:

> " 'In determining whether the invention as a whole would have been obvious under 35 USC 103, we must first delineate the invention as a whole. In delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in question...but also to those properties of the subject matter which are inherent in the subject matter **and** are disclosed in the specification....Just as we look to a chemical and its properties when we examine the obviousness of a composition of matter claim it is this invention as a whole, and not some part of it, which must be obvious under 35 U.S.C. 103.' *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6,8 (CCPA 1977)." (emphasis in the original reported text but omitted in the quote appearing in the Action)".

The court in *Antonie* went on to find:

> "The controlling question is simply whether the differences...between the prior art and appellant's invention as a whole are such that appellant's invention as a whole would have been obvious. The answer is no. It is impossible to recognize from the experiment taught by El-Naggar that 'treatment capacity' is a function of 'tank volume'...."

The same conclusion arises in the present case. Thus, the present invention as a whole (i.e. a method treating one of the recited congenital mitochondrial diseases by administration of an effective amount of a pyrimidine nucleotide precursor) would not have been obvious to one of ordinary skill, because of the absence of any suggestion of this in Page or Von Borstel, to recognize that treatment of one of the recited congenital mitochondrial diseases could be achieved by administration of an effective amount of a pyrimidine nucleotide precursor.

On pages 3 and 4 of the Action, it is stated

> "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. In construing process claims and references, it is the identity of manipulative operations which leads to finding of obviousness."

No legal authority is provided for this proposition. Applicants disagree that it is "the identity of manipulative operations which leads to finding of obviousness". Rather, the controlling question is "simply whether the differences...between the prior art and appellant's invention as a whole are such that appellant's invention as a whole would have been obvious." *In re Antonie, supra.* It is wrong to ignore the fact that patients with different conditions are being treated. Moreover, inherency is not an appropriate consideration in the context of obviousness ("...that which may be inherent is not necessarily known. Obviousness cannot be predicated on that which is unknown" *In re Spormann and Heinke*, 363 F.2d 444, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966).

On page 6 of the Action, it is stated:

> "Mere recitation of newly-discovered function or property, inherently possessed by things in prior art, does not cause claim drawn to those things to distinguish over prior art; Patent Office can require applicant to

> prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; this burden of proof is applicable to product and process claims reasonably considered as possessing allegedly inherent characteristics. Patent and Trademark Office does not have facilities for examining and comparing applicant's claimed invention with the prior art, and thus applicants have the burden of persuasion to make some comparison with the prior art in order to establish unexpected results."

Office again, the reference in the above statement to inherency in the context of obviousness is improper, for the reasons discussed above. The proper inquiry is whether the differences between the prior art and the claimed invention as a whole are such that appellant's invention as a whole would have been obvious. In this case, the answer is no, because the present invention viewed as a whole, including that which is disclosed in the present specification, would not have been rendered obvious by Page, either taken alone or in combination with Von Borstel. Those two disclosures contain no disclosure or suggestion of a method of treating a congenital mitochondrial disease selected from those recited in the claims by administering an effective amount of a pyrimidine nucleotide precursor.

The Action contains extensive quotations from Page and from the present specification. However, as unrelated diseases can have overlapping symptoms, it follows that the effectiveness of a particular drug in treating a symptom in one disorder does not necessarily, or even generally, imply that the drug will be useful in treating other diseases with similar symptoms. Numerous examples of this have been earlier provided in this case. Thus, for example, epilepsy or related seizure disorders may be caused by tumors, poisons, mitochondrial defects, or simply self-amplifying circuits of

neural activity without other organic defects causing the seizures. Seizure episodes in a susceptible person can be triggered by progesterone deficits, e.g. associated with the menstrual cycle. Although the clinical symptoms – seizures – may look similar, the treatments will vary according to the underlying problem. Valproate (Depakote) is a widely-used anti-seizure medication, but it can actually exacerbate seizures (and other manifestations of mitochondrial disease) caused by mitochondrial deficits, due to its inhibitory effect on mitochondrial respiration. For someone with seizures triggered by a progesterone deficit, progesterone or an analog thereof is more appropriate than increased doses of other anti-seizure medications, which have debilitating side effects at higher doses. Some seizure disorders associated with foci of hyperexcitable neurons are best treated with electrodes inserted into the brain, which would be inappropriate for seizures caused by metabolic deficits. Copies of literature references in support of this were submitted with the previous response.

Another example of a condition which can arise from different causes is arthritis. Pain in the joints can be caused by autoimmune attack (rheumatoid arthritis, psoriatic arthritis, or lupus-associated), osteoarthritis, infections, e.g. lime disease, gout, deposition of antibody complexes, etc. All of these disorders may present with joint pain as a predominant symptom, but the appropriate treatments are very different for each of these different diseases that underlie similar symptoms, e.g. anti-TNF therapies for rheumatoid arthritis, B-Cell suppressors for Lupus, nonsteroidal anti-inflammatory drugs for osteoarthritis, antibiotics for Lyme disease, allopurinol for gout. Again, the previous response was accompanied by literature evidence in support of this.

Many other examples are possible in which symptoms themselves provide inadequate information for determining their cause and appropriate treatment. Developmental delays may arise from a variety of underlying causes, including metabolic defects such as phenylketonuria, lead or mercury poisoning, epilepsy, or a variety of genetic defects. A diet low in phenylalanine helps patients with phenylketonuria (in which an enzyme deficiency prevents phenylalanine metabolism), but is useless in other conditions involving developmental delay or seizures. Lead and mercury poisoning can perhaps helped by administration of chelating agents which are useless in diseases not caused by heavy metals. Antiepileptic drugs like valproate or lamictal can help developmental delays secondary to disruptions in brain function caused by seizures, but may be detrimental in disorders not caused by seizures.

As earlier argued in the record of this case, the relationship between 5'-nucleotidase excess and symptoms in the children described by Page et al. is not clear. As the authors point out, the disorder is not associated with actual uridine nucleotide deficits (and the symptoms do not match those of the only known pyrimidine deficit disorder, Orotic Aciduria). Uridine and related pyrimidine compounds were initially tested in these patients because the first one identified presented with megaloblastic anemia (a primary symptom of orotic aciduria), which was later attributed to her anti-seizure medication. The finding that uridine was helpful was actually fortuitous and does provide a basis for asserting that uridine would be helpful in similar symptoms or symptom complexes associated with other diseases.

In addition, the cited Page et al paper is not the first publication of the use of uridine to treat 5'-nucleotidase excess. This was published earlier in Page, et al., "A

Syndrome of Megaloblastic Anemia, Immunodeficiency, and Excessive Nucleotide Degradation," in Purine and Pyrimidine Metabolism in Man VII, Part B, Harkness, et al. eds (1991) pp. 345-348 (of record). The fact that between 1991 and the subject invention no one used uridine compounds to treat pathophysiological consequences of mitochondrial respiratory chain dysfunction is further evidence of its nonobviousness.

In view of the above, it is believed that a *prima facie* case of obviousness has not been generated in this case. Withdrawal of the obviousness rejection is respectfully requested.

Favorable action is awaited.

Respectfully submitted,

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